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ORIGINAL REPORT

Association of Age With Survival in Patients With Metastatic Colorectal Cancer: Analysis From the ARCAD Clinical Trials Program

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ABSTRACT

Purpose
This study addressed whether age is prognostic for overall survival (OS) or progression-free survival (PFS) in patients with metastatic colorectal cancer (mCRC).

Patients and Methods
A total of 20,023 patients from 24 first-line clinical trials in the ARCAD (Aide et Recherche en Cancérologie Digestive) database were analyzed. Primary age effects and interactions with age, sex, performance status (PS), and metastatic site were modeled using Cox proportional hazards stratified by treatment arm within study.

Results
Of total patients, 3,051 (15%) were age ≤ 50 years. Age was prognostic for both OS ($P < .001$) and PFS ($P < .001$), with U-shaped risk (ie, highest risk was evident in youngest and oldest patients). Relative to patients of middle age, the youngest patients experienced 19% (95% CI, 7% to 33%) increased risk of death and 22% (95% CI, 10% to 35%) increased risk of progression. The oldest patients experienced 42% (95% CI, 31% to 54%) increased risk of death and 15% (95% CI, 7% to 24%) increased risk of progression or death. This relationship was more pronounced in the first year of follow-up. Age remained marginally significant for OS ($P = .08$) when adjusted for PS, sex, and presence of liver, lung, or peritoneal metastases, and age was significant in an adjusted model for PFS ($P = .005$). The age effect did not differ by site of metastatic disease, year of enrollment, type of therapy received, or biomarker mutational status.

Conclusion
Younger and older age are associated with poorer OS and PFS among treated patients with mCRC. Younger and older patients may represent higher-risk populations, and additional studies are warranted.

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INTRODUCTION

In the United States in 2013, there were 142,570 new occurrences of colorectal cancer (CRC) and 51,370 deaths resulting from this disease.[1] Median age at diagnosis of CRC is 72 years, and 28% of patients are age > 80 years.[2] In the general population, those patients age < 50 years comprise only 4.6% of individuals diagnosed with CRC. Although CRC is rare in young adults, the incidence in the younger population has increased recently, even though the incidence has declined among older patients.[3] The incidence of CRC has increased approximately 1.5% per year among those age < 50 years, with the most striking increases among those age 20 to 29 years (men, 5.2% per year; women, 5.6% per year).[3] Although this could be ascribed to heredity, a recent population-based sample of patient cases of young-onset CRC found that although germline mutations in *MLH1*, *MSH*, and/or *MSH6* were more prevalent than those reported for all patients with CRC, individuals with those mutations only comprised 5% to 7% of patient cases of young-onset CRC.[4,5] Therefore, it seems that a majority of CRCs in younger patients are sporadic in nature.

In younger patients, CRC tends to present more commonly as stage III or IV disease, which may reflect differing biology, later diagnosis because of the rarity of this condition in that age group, and/or less surveillance in that age group.[6] In younger patients, there seems to be a higher frequency of tumors with poor differentiation, T4 disease stage, and vascular invasion.[7,8] A recent retrospective review of nine phase III chemotherapy

trials in patients with advanced CRC assessed outcomes in younger versus older patients, as defined by age < 40 or > 50 years.[9] Although younger age was associated with shorter progression-free survival (PFS), there was no difference in overall survival (OS) or response rates for younger versus older patients, and younger patients derived similar benefit from combination chemotherapy. This study did not include trials with biologic agents. Several smaller cohort studies have reported similar results with regard to OS.[10-12]

In this study, we used the ARCAD (Aide et Recherche en Cancérologie Digestive) Foundation database to assess outcomes as a function of age, and we describe the analyses of the pooled results of 24 first-line randomized metastatic CRC trials. In contrast to prior studies, age was evaluated as a continuous variable rather than using a prespecified cut point defining younger versus older patients.

PATIENTS AND METHODS

All patients enrolled onto first-line phase III trials contained in the ARCAD database with recorded age ≥ 18 years were eligible for analysis. The ARCAD CRC database integrates individual patient–level data from existing clinical trials in CRC for the purpose of evaluating the appropriate means (eg, prognostic factors, end points, and timing of assessments) to conduct future trials in CRC and establishing a standing resource for future investigations.

The primary end points were OS, defined as time from random assignment to death as a result of any cause, and PFS, defined as time from random assignment to the earlier of death or disease progression. Cox proportional hazards models stratified by treatment arm within study were used to build prognostic models for OS and PFS with age as a key covariate. Within the Cox models, age in years was treated as a continuous (rather than categorized) variable and modeled using restricted cubic splines to allow for possible nonlinearity of the age effect on the log-relative hazard scale.[13] Null hypotheses of no effect of age on outcome and linearity of the age effect on the log-relative hazard were tested, where in either case $P < .05$ indicated statistical significance. Where nonlinearity was found to be nonsignificant, age was treated as a continuous variable in the standard linear fashion. Subsequently, multivariable Cox models were used to test the age effect adjusted by or interacting with sex, performance status (PS), targeted versus nontargeted therapy among studies with targeted versus nontargeted therapy randomization, targeted therapy class (antiangiogenesis or anti–epidermal growth factor receptor [EGFR; *KRAS* wild type only]), biomarkers (*KRAS*, *BRAF*), and presence or absence of liver, lung, or peritoneal metastases. Differences in the age distribution by each categorical variable were visually explored via histograms and tested using *t* tests, given the approximate normality of age. A possible time trend was considered using the year of enrollment of each patient. Interactions associated with $P < .01$ were deemed significant if clinically relevant age-by-factor relationships were observed on visual inspection of relevant plots. Cox proportional hazards models investigating the age effect specific to the first year of follow-up were also performed. Patients with missing biomarker or metastatic site data, where unavailable data were generally the result of

Table 1. ARCAD Trials Used in Analysis

Trial	Years of Accrual	Frontline Treatment Arms	No. of Patients
03-TTD-01*	2002 to 2004	FUOX *v* CAPOX	342
AGITG (MAX)*	2005 to 2007	Capecitabine *v* capecitabine + bevacizumab *v* capecitabine + bevacizumab + mitomycin	471
AIO22*†	2002 to 2004	FUOX *v* CAPOX	470
AVF2107g*	2000 to 2002	IFL *v* IFL + bevacizumab	923
AVF2192g*	2000 to 2002	FU *v* FU + bevacizumab	209
BICC-C*	2003 to 2004	mIFL ± bevacizumab *v* FOLFIRI ± bevacizumab *v* capecitabine + irinotecan	532
C97-3*	1997 to 1999	FOLFOX6 *v* FOLFIRI	220
CAIRO1*†	2003 to 2004	Capecitabine *v* capecitabine + irinotecan	820
CAIRO2*†	2005 to 2006	CAPOX + bevacizumab *v* CAPOX + bevacizumab + cetuximab	743
COIN*†	2005 to 2008	FOLFOX *v* FOLFOX + cetuximab *v* intermittent FOLFOX	2,418
FIRE II (CIOX)*†	2004 to 2006	XELOX + cetuximab *v* capecitabine + irinotecan + cetuximab	177
FOCUS*	2000 to 2003	FU *v* combination chemotherapy	2,101
FOCUS II*	2004 to 2006	FU *v* FOLFOX *v* capecitabine *v* CAPOX	397
GONO*	2001 to 2005	FOLFOX + irinotecan *v* FOLFIRI	244
HORG 99.30*†	2000 to 2004	FOLFOX + irinotecan *v* FOLFIRI	283
HORIZON II*	2006 to 2010	FOLFOX+ CAPOX + cediranib *v* FOLFOX + CAPOX	1,076
HORIZON III*	2006 to 2009	FOLFOX + cediranib *v* FOLFOX + bevacizumab	1,612
MACRO†	2006 to 2008	XELOX + bevacizumab (maintenance) *v* bevacizumab (maintenance)	476
N016966*	2004 to 2005	FOLFOX + CAPOX + bevacizumab *v* FOLFOX + CAPOX	2,035
N9741*	1999 to 2001	IFL *v* FOLFOX *v* irinotecan + oxalipltin	1,415
OPTIMOX 1*	2000 to 2002	FOLFOX4 *v* FOLFOX7 (maintenance)	621
OPTIMOX 2*	2004 to 2006	mFOLFOX7 *v* mFOLFOX7 (with complete stop)	202
PACCE (C249)†	2005 to 2006	Chemotherapy + bevacizumab *v* chemotherapy + bevacizumab + panitumumab	1,053
PRIME (C203)†	2006 to 2008	FOLFOX *v* FOLFOX + panitumumab	1,183
Total ARCAD			20,023

Abbreviations: AGITG, Australasian Gastro-Intestinal Trials Group; AIO, Arbeitsgemeinschaft Internistische Onkologie; ARCAD, Aide et Recherche en Cancérologie Digestive; AVF, anastomotic-vaginal fistula; BICC, Breast Cancer in City and Country; CAIRO, Capecitabine, Irinotecan, and Oxaliplatin in Advanced Colorectal Cancer; CAPOX, capecitabine plus oxaliplatin; COIN, Continuous Chemotherapy Plus Cetuximab, or Intermittent Chemotherapy With Standard Continuous Palliative Combination Chemotherapy With Oxaliplatin and a Fluoropyrimidine in First-Line Treatment of Metastatic Colorectal Cancer; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil; FUOX, fluorouracil plus oxaliplatin; GONO, Gruppo Oncologico Nord Ovest; HORG, Hellenic Oncology Research Group; IFL, irinotecan, leucovorin, and fluorouracil; m, modified; MACRO, Maintenance in Colorectal Cancer; PACCE, Panitumumab Advanced Colorectal Cancer Evaluation; XELOX, capecitabine plus oxaliplatin.

*Contributed to analyses involving metastatic sites.

†Contributed to biomarker (*KRAS*, *BRAF*) analyses.

noncollection from specific ARCAD trials, were excluded from relevant analyses.

RESULTS

Description of Available Data

Descriptions of the ARCAD first-line trials are listed in Table 1. In total, 20,023 patients from 24 first-line trials with available age, PFS, and OS data were considered for the analyses. Mean age was 62 years (interquartile range, 55 to 69 years); 698 patients (4%) were age < 40 years, and 2,715 patients (14%) were age < 50 years. Patient sex was distributed as 38% female (n = 7,685) and 62% male (n = 12,323); sex was not available for 19 patients. Most patients (10,427; 53%) had PS of 0 at baseline, with 8,502 patients (43%) with PS of 1 and 860 patients (4%) with PS ≥ 2; PS was missing for 234 patients. Mean age was statistically but not clinically different by sex ($\bar{X}_M = 62$; $\bar{X}_F = 60$; $P < .001$; Fig 1A); mean age was statistically different across levels of PS ($\bar{X}_{PS0} = 61$; $\bar{X}_{PS1} = 62$; $\bar{X}_{PS2+} = 65$; $P < .001$; Fig 1B). Using all available follow-up, median PFS was 8.1 months, and median OS was 17.9 months, with these outcomes distributed as shown in Appendix Fig A1 (online only). Median follow-up among surviving patients was 18 months.

Primary Age Analyses

In a univariable Cox model for OS, age was a significant predictor of OS ($P < .001$) and significantly nonlinear ($P < .001$) with U-shaped risk, where the youngest and oldest patients showed worse survival than patients of middle age (Fig 2A). Specifically, compared with patients approximately 57 years of age (reference age associated with lowest risk), the youngest patients (those near age 18 years) showed a 19% (95% CI, 7% to 33%) increased risk of death during follow-up, whereas the oldest patients (those near age 90 years) showed a 42% (95% CI, 31% to 54%) increased risk of death, with less risk increase between the age extremes. This relationship remained significant ($P < .001$) when adjusted for sex and PS. The effect of age on OS was even more pronounced during the first year ($P < .001$; Fig 3A). Specifically, compared with patients near age 57 years, the youngest patients showed a 28% (95% CI, 10% to 50%) increased risk of death during the first year of follow-up, whereas the oldest patients showed a 71% (95% CI, 53% to 92%) increased risk of death, with less increase in risk between the age extremes.

Univariable results were similar for PFS ($P < .001$; Fig 2B). Compared with patients age approximately 61 years (with least risk of progression or death), the youngest patients (those near age 18 years) showed a 22% (95% CI, 10% to 35%) increased risk of progression or death, whereas the oldest patients (near age 90 years) showed only a 15% (95% CI, 7% to 24%) increased risk of progression or death. This relationship also remained significant ($P = .002$) when adjusted for sex and PS. The effect of age on PFS was similarly more pronounced during the first year ($P < .001$; Fig 3B). Specifically, compared with patients near age 61 years, the youngest patients showed a 29% (95% CI, 15% to 44%) increased risk of progression or death during the first year of follow-up, whereas the oldest patients showed a 19% (95% CI, 10% to 30%) increased risk of progression or death.

Age Effect by PS and Sex

The age effect did not differ significantly by PS for either OS (interaction $P = .28$) or PFS (interaction $P = .48$), although PS was itself prognostic for OS and PFS, with increased risk associated with increased PS, as shown in Figures 2C and 2D, respectively. Within the

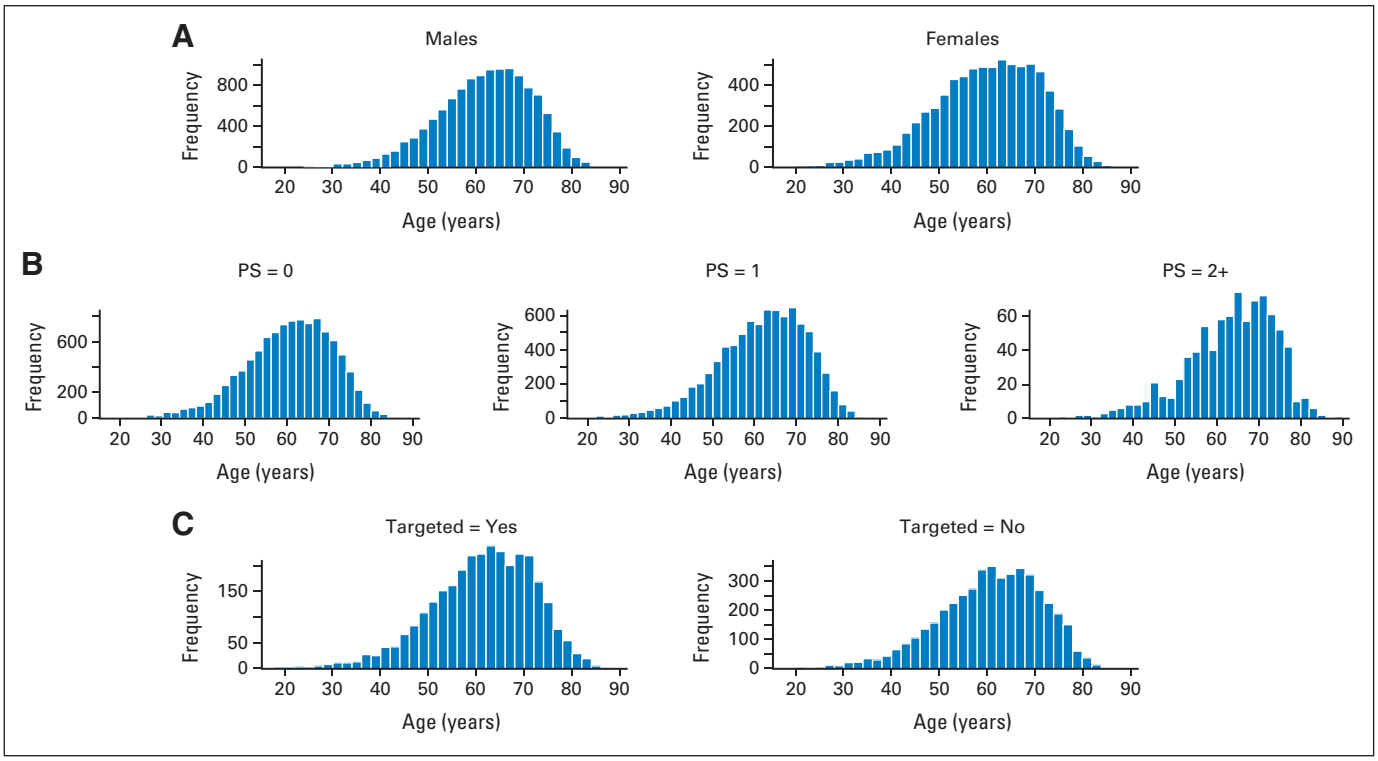

Fig 1. Distribution of age by (A) sex, (B) performance status (PS), and (C) targeted versus nontargeted therapy.

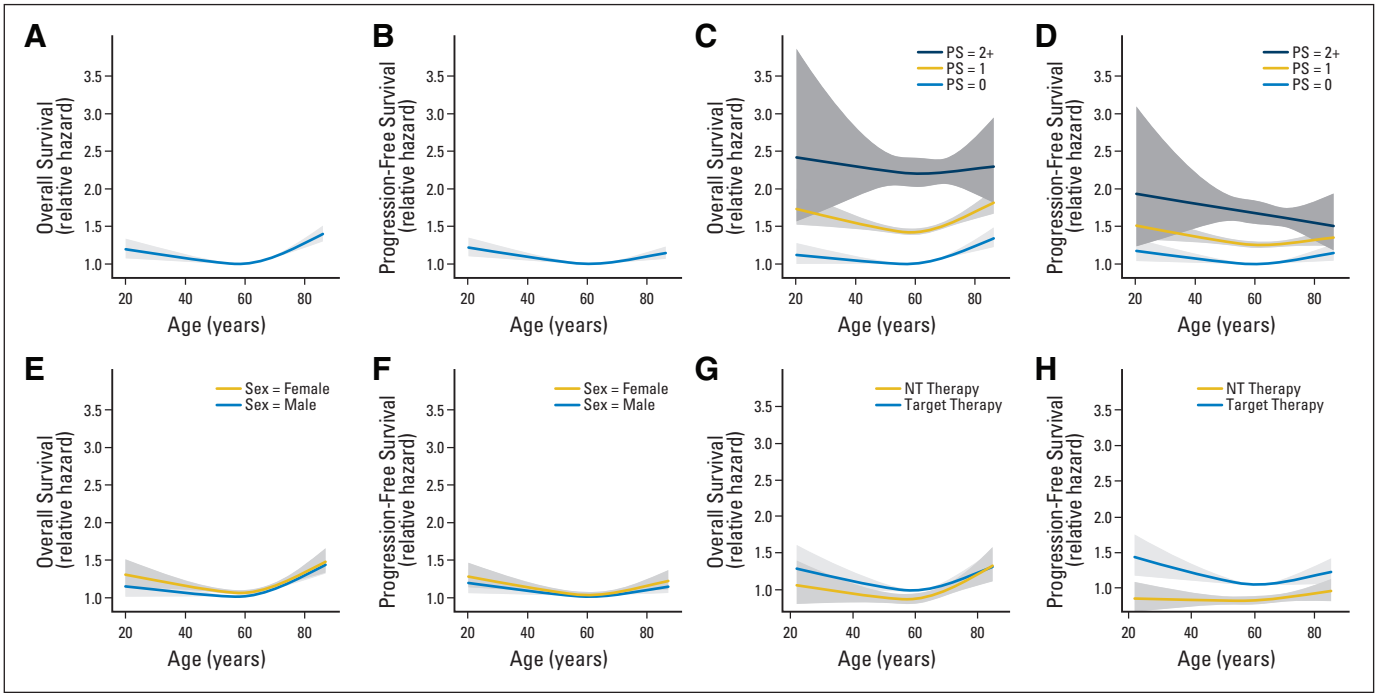

Fig 2. Risk of (A) death and (B) progression or death as nonlinear function of age, with highest risk at young and old extremes; risk of (C) death and (D) progression or death as function of age according to performance status (PS); risk of (E) death and (F) progression or death as function of age according to sex; (G) risk of death and (H) progression or death as function of targeted or nontargeted therapy. Figures based on all available follow-up. Age-by-sex interaction was not significant.

first year of follow-up, the age-by-PS interactions remained nonsignificant for OS ($P = .06$; Fig 3C) and PFS ($P = .70$; Fig 3D). Age did not significantly interact with sex for either OS (interaction $P = .62$; Fig 2E) or PFS (interaction $P = .85$; Fig 2F).

Age Effect by Presence Versus Absence of Liver, Lung, or Peritoneal Metastases

Twenty-four studies listed in Table 1 contributed data on the presence versus absence of liver (n = 17,075), lung (n = 16,455), and/or peritoneal metastases (n = 9,638). The distribution of patient age did not differ significantly by presence versus absence of disease in any of these sites (Appendix Figs 2A to 2C, online only). Although there were no statistically significant age-by-site interactions for either end point, some sites showed clinical prognostic influence (Figs 4A to 4F), with generally increased risk of progression and/or death with presence of metastases. A multivariable model for OS containing terms for age, PS, sex, and presence versus absence of each of the metastatic sites (n = 9,630) is summarized in Table 2. When adjusted for clinical variables and metastatic sites, age was only marginally significant for OS ($P = .08$) but remained significant for PFS ($P = .005$). In both adjusted models, the contribution of age was found to be linear, with (marginally significant) increased risk of death for older patients and significantly increased risk of progression or death for younger patients. Presence of any of the metastatic sites was associated with increased risk for either end point, and male sex was associated with decreased risk of death.

Age Effect by Therapy Class, Biomarker Status, and Time

The distribution of patient age did not differ significantly by targeted versus nontargeted therapy (n = 7,255; Fig 1C). The age effect on OS was not different according to treatment with nontargeted versus targeted therapy (interaction $P = .248$; Fig 2G); similarly, there was no difference in the age effect by therapy type for PFS (interaction $P = .462$; Fig 2H). The prognostic effect of age also did not differ according to class of targeted therapy (antiangiogenesis or anti-EGFR) for either OS (interaction $P = .093$) or PFS (interaction $P = .637$). The distribution of age did not differ according to *KRAS* (n = 5,564) or *BRAF* (n = 2,620) mutational status, and furthermore, the prognostic effect of age did not differ by either *KRAS* (both OS and PFS interaction $P = .67$) or *BRAF* (OS, interaction $P = .94$; PFS, interaction $P = .72$) mutational status. No significant time trend was present after accounting for patient age (OS, $P = .774$; PFS, $P = .073$).

DISCUSSION

CRC in young adults is a rare but serious diagnosis, and the incidence in younger patients has increased recently despite a decline in overall incidence.[1] Although outcomes for adolescents and young adults have been shown to be worse for several malignancies, epithelial neoplasms have not been well studied.[14,15] Young patients with CRC present with later-stage disease (stage III or IV); however, it is unclear whether this reflects differing biology or simply the low rate of CRC screening studies performed in this age group. It should be noted that younger patients also have a greater incidence of poor differentiation and lymphovascular invasion than older patients with CRC, suggesting the possibility that the disease in younger patients has more aggressive features.[6]

In contrast to prior studies, our analyses revealed that age was a significant predictor of OS, with the youngest and oldest patients showing worse survival than patients of middle age, with similar results seen for PFS.[9-11] Reasons for this difference may include a

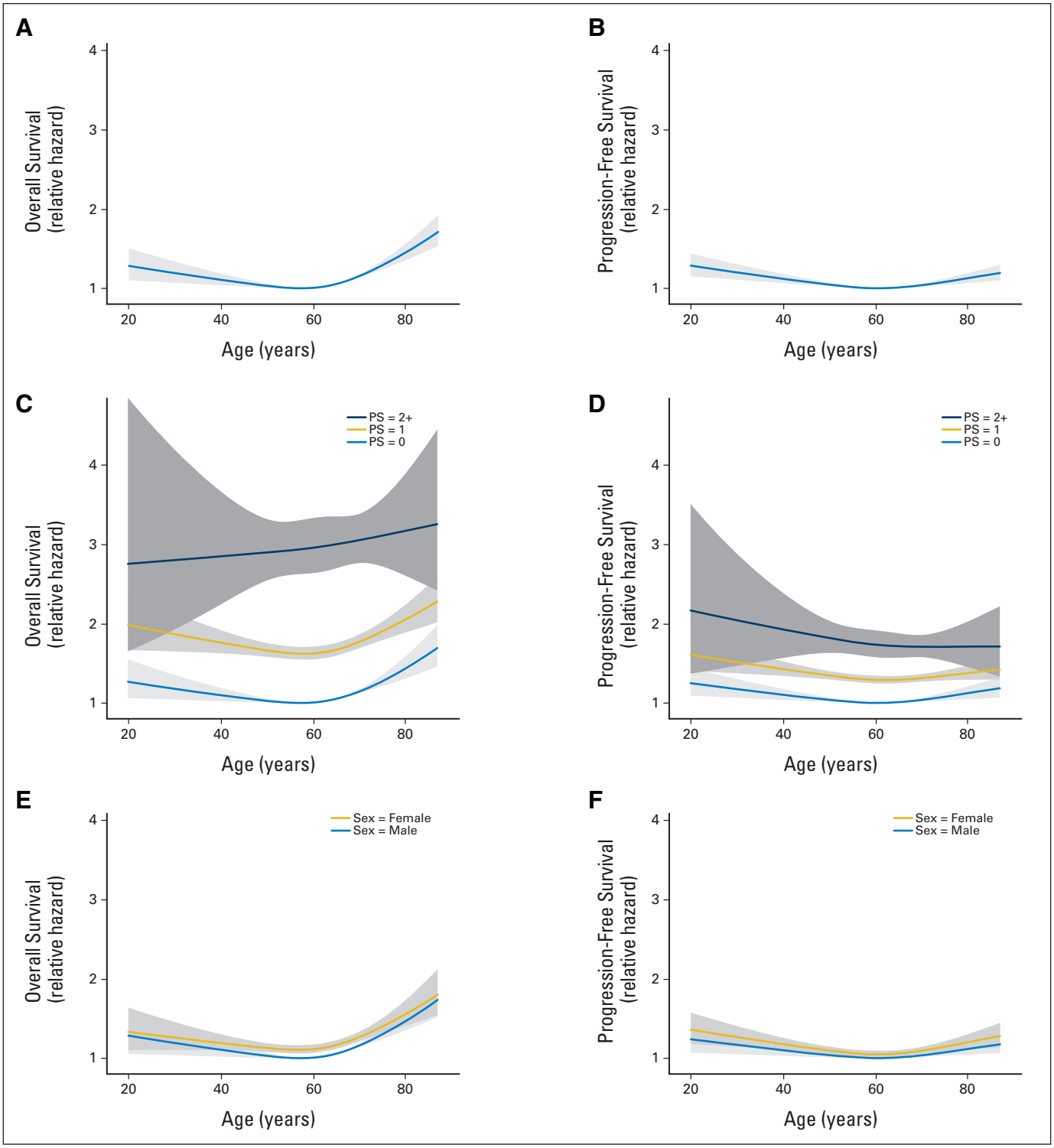

Fig 3. Risk of (A) death and (B) progression or death as nonlinear function of age, with highest risk at young and old extremes; risk of (C) death and (D) progression or death as function of age according to performance status (PS); and risk of (E) death and (F) progression or death as function of age according to sex. Analysis and figures based on first year of follow-up. Age-by-sex interaction was not significant.

greater number of patients included in this analysis age $<$ 40 years (698 patients) and age evaluated as a continuous variable instead of a prespecified cut point (ie, age $<$ 40 or $>$ 40 years). Unlike prior studies, this analysis also includes data from trials using biologic agents, which may also play a role in OS and PFS. Prior studies have also used older databases with less effective treatment regimens, whereas a majority of the studies included in this analysis completed accrual $<$ 10 years before this analysis. For OS, patients age 57 years

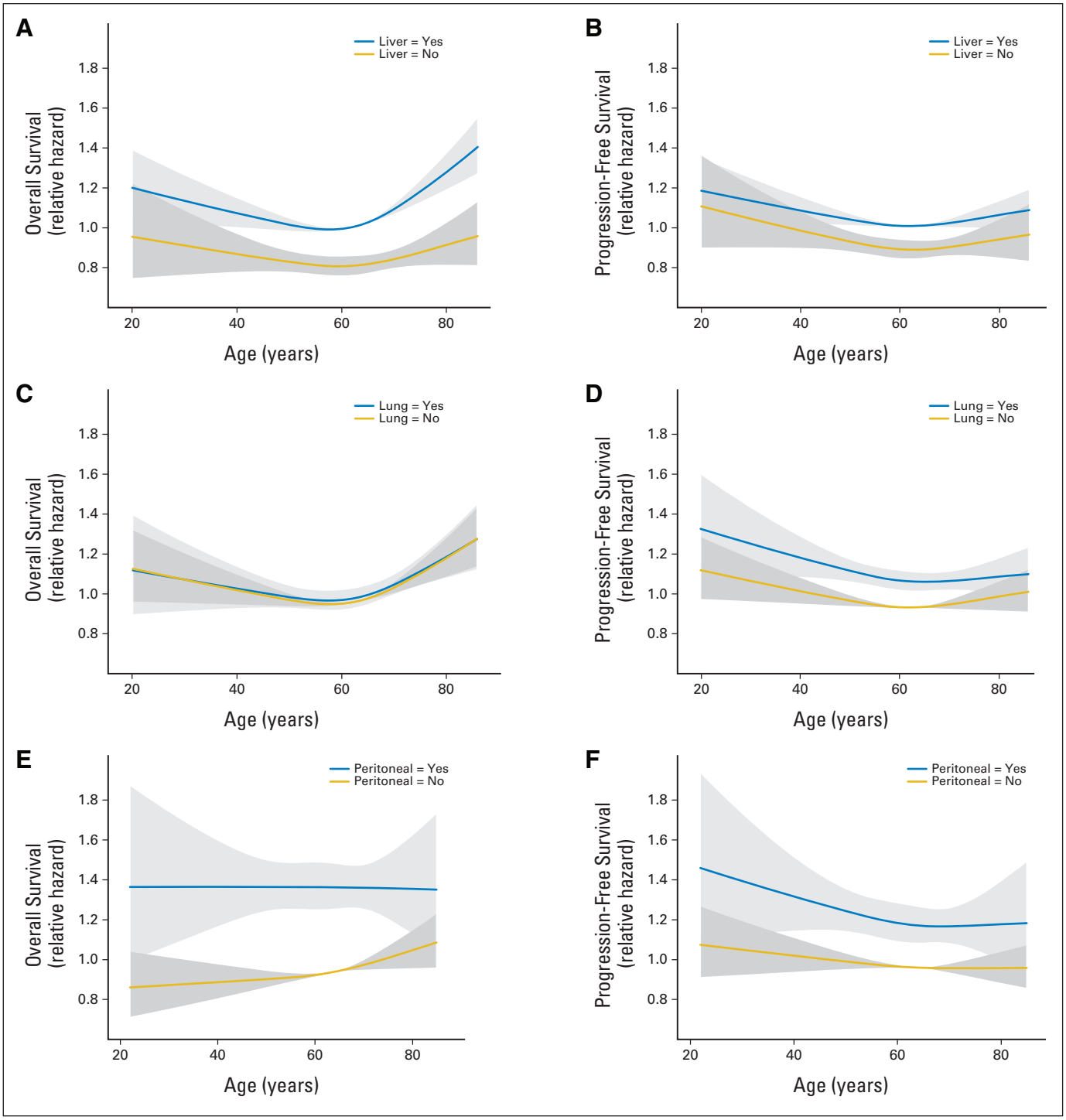

Fig 4. Risk of (A) death and (B) progression or death as nonlinear function of age according to presence versus absence of liver metastases; risk of (C) death and (D) progression or death as function of age by presence versus absence of lung metastases; and risk of (E) death and (F) progression or death as function of age by presence versus absence of peritoneal metastases. Figures based on all available follow-up. No age-by-site interactions were significant.

were associated with the lowest risk, and the youngest patients (those near age 18 years) showed a 19% increased risk of death during follow-up, with a decrease in relative risk as middle age is approached. This finding is particularly concerning when considering that younger patients may have fewer comorbidities and may be better able to tolerate more intense chemotherapy regimens. The effect of age was more pronounced during the first year of follow-up, suggesting that there may be a subset of younger patients with CRC who have a poor prognosis compared with patients of middle age, and that effect on OS is seen within the first year. The youngest patients also had a 22% increased risk of progression relative to patients of middle age, suggesting decreased efficacy of first-line chemotherapy. The effect of

Table 2. Multivariable Models for OS and PFS

		OS				PFS			
Variable	%	Coefficient	SE	HR	*P*	Coefficient	SE	HR	*P*
Age	—	0.002	0.001	1.00	.0831	−0.003	0.001	0.99	.005
Sex					< .001				.116
Female	38	—	—	—		—	—	—	
Male	62	−0.085	0.025	0.92		−0.035	0.023	0.97	
PS					< .001				< .001
0	53	—	—	—		—	—	—	
1	43	0.352	0.025	1.42		0.207	0.023	1.23	
2+	4	0.769	0.048	2.16		0.456	0.046	1.58	
Liver metastases					< .001				< .001
No	22	—	—	—		—	—	—	
Yes	78	0.262	0.030	1.30		0.139	0.026	1.15	
Lung metastases					.0035				< .001
No	63	—	—	—		—	—	—	
Yes	37	0.075	0.023	1.08		0.171	0.023	1.19	
Peritoneal metastases					< .001				< .001
No	84	—	—	—		—	—	—	
Yes	16	0.378	0.034	1.46		0.232	0.032	1.26	

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PS, performance status.

young age on PFS was also seen in a prior pooled analysis.[9] There was no age effect on OS or PFS in patients treated with targeted or nontargeted therapy, and the distribution of age did not differ by *KRAS* or *BRAF* mutational status.

The risk of death was significantly increased in older patients, which may be expected given the possibility of less-fit patients, decreased overall life expectancy, and inability to tolerate aggressive chemotherapy regimens. Unlike the youngest patients, who showed a similar increase in OS and PFS risk, the oldest patients had a 42% increased risk of death but only a 15% increased risk of progression. This difference may be secondary to increased comorbidities and inability to tolerate aggressive chemotherapy regimens, as opposed to ineffectiveness of first-line regimens or more aggressive biology, although further study in this patient population is needed.

The effect of age on OS or PFS did not differ significantly by PS. It should be noted that there are inherent biases in assigning PS to younger versus older patients, because younger patients are more likely to have a decreased PS attributable to CRC, whereas an older patient may be assigned a decreased PS because of other comorbidities and lower baseline functional status.

There were no significant interactions between age and presence versus absence of liver, lung, or peritoneal metastases for either OS or PFS, and there was no difference in age distribution according to presence versus absence of metastases at any site. Therefore, although risk of OS or PFS events seems higher in younger and older patients versus those of middle age, this difference does not seem to be related to site of metastatic disease.

In summary, this pooled analysis demonstrates that younger and older patients with metastatic CRC may be at increased risk of death and progression, suggesting that both younger and older patients with metastatic CRC could represent a higher-risk population. Although younger patients are typically healthier, with fewer comorbidities, than older patients, their outcomes are not necessarily improved, which may reflect differing biology or presence of greater tumor burden at the time of presentation because of decreased screening rates in younger patients. When considering treatment regimens for older patients, risks and benefits of toxicities must be taken into consideration. Younger and older patients with metastatic CRC may be considered for substratification in future clinical trials because of their differences in outcome, and further study of potential genetic and biologic differences is warranted in these patient populations, in addition to more active participation in clinical studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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GLOSSARY TERMS

BRAF V600E: the most common oncogenic mutation of BRAF in cancer. The V600E aminoacid change results in constitutive activation of the BRAF kinase and promotes cell transformation.

K-RAS: the gene that encodes K-RAS, a protein that is a member of the small GTPase superfamily, in which a single amino acid substitution results in an activating mutation. Alternative splicing gives rise to variants encoding two isoforms that differ in the C-terminal region.

biomarker: a functional biochemical or molecular indicator of a biologic or disease process that has predictive, diagnostic, and/or prognostic utility.

epidermal growth factor receptor (EGFR): a member of a family of receptors (HER2, HER3, HER4 are other members of the family) that binds to the EGF, TGF-α, and other related proteins, leading to the generation of proliferative and survival signals within the cell. EGFR (also known as HER1) also belongs to the larger family of tyrosine kinase receptors and is generally overexpressed in several solid tumors of epithelial origin.

MLH1 (MutL homolog 1): a DNA mismatch repair enzyme. MLH1 is responsible for overall fidelity of DNA replication.

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Appendix

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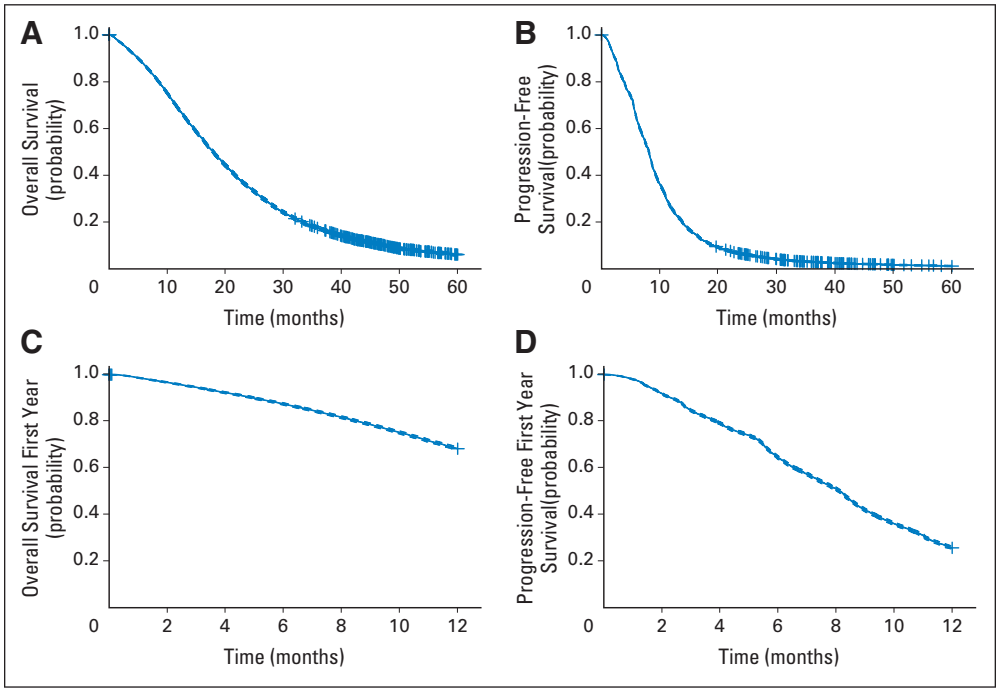

Fig A1. Kaplan-Meier plots for overall survival (A, C) and progression-free survival (B, D), with full follow-up (A, B) and restriction to 1 year of follow-up (C, D).

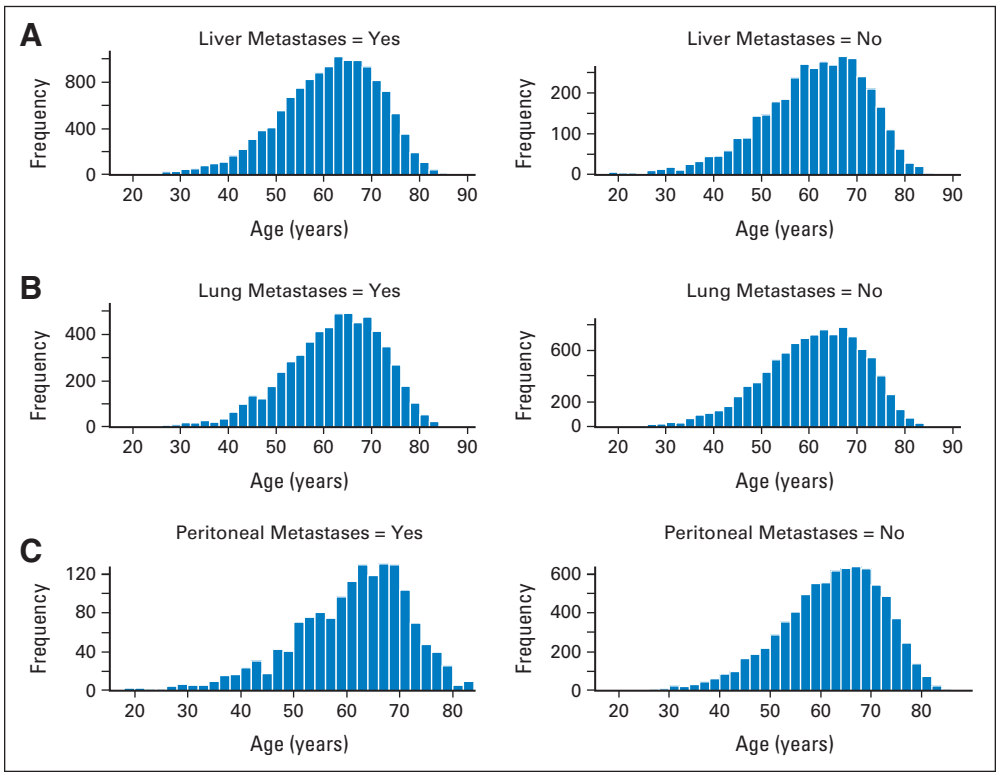

Fig A2. Distribution of age by presence versus absence of (A) liver, (B) lung, and (C) peritoneal metastases.